REMARKS

Entry of the claim amendments is respectfully requested. No new matter is added. Applicant notes with appreciation the Examiner's suggestions in the Official Action mailed October 30, 2002.

Applicant has amended the claims in response to the rejection pursuant to 35 U.S.C. § 112, second paragraph. Specifically, claim 2 has been amended to more clearly specify that the method claimed is directed to treating or preventing diarrhea in a mammal, comprising administering a therapeutically effective amount of viable *E. coli* strain DSM 6601. Independent claim 4 has been amended to more clearly specify that the method claimed is directed to preventing diarrhea. In addition, new claim 17 has been added, which recites a method for treating or preventing intestinal colonization of pathogenic fungi in a mammal. Support for the amendments and new claims are found in the original specification. Accordingly, no new matter has been added.

With respect to the Examiner's contention that claims 2 and 4 are vague and indefinite because it is unclear what is intended by "mediated by . . . colonization," and how such diarrhea can be prevented in every instance, Applicant submits that the claims as amended are believed to overcome the Examiner's rejection. Moreover, if the Examiner maintains her inquiry as to how the diarrhea can be "prevented in every instance," Applicant submits that it is not necessary to show that the claimed method will prevent diarrhea "in every instance." Similar to the numerous patents directed to methods of treating and preventing cancer, it is plain that an Applicant is not required to be held to such a high standard. As to the Examiner's inquiry as to how one would determine which diarrhea is prevented, Applicant has amended claims 2 and 4 to delete

reference to anti-fungal activity, as suggested by the Examiner, therefore rendering this inquiry moot.

As to the remaining rejections under 35 U.S.C. § 112, second paragraph, Applicant has amended the claims in view of the Examiner's comments and suggestions. Specifically, Applicant has amended the claims to recite that a therapeutically effective amount of viable *E. coli* strain DSM 6601 is administered. Accordingly, reconsideration and withdrawal of the § 112 rejections are respectfully requested.

Claims 2-5 are rejected under 35 U.S.C. § 102(b) as being anticipated by *Hockertz* or *Lodinova-Zadnikova et al.*, or under 35 U.S.C. § 102(a) as being anticipated by DE 196 37 936. The Examiner maintains her position that *Hockertz* discloses a one-step administration of DSM 6601 to mice and would inherently prevent diarrhea in these animals. The Examiner also contends that *Lodinova-Zadnikova et al.* discloses a one-step administration of DSM 6601 to humans, and that this administration would inherently prevent fungi-mediated diarrhea. Further, the Examiner contends that DE 196 37 936 teaches the administration of NISSLE 1917 (DSM 6601) and nystatin to treat intestinal *Candida* infection. In this regard, the Examiner states that Applicant's claimed methods are open to the administration of other drugs, such as nystatin, and are therefore anticipated by the cited reference.

Initially, Applicant notes that at the Examiner's suggestion, the claims have been amended to recite the administration of a therapeutically effective amount of viable *Escherichia coli* strain DSM 6601. In view of these amendments, it is clear that none of the references teach the claimed methods of treating or preventing the intestinal colonization of pathogenic fungi, or diarrhea caused by the intestinal colonization of pathogenic fungi, by administering an effective

amount of viable *E. coli* strain DSM 6601 either directly or inherently.

With respect to *Hockertz*, Applicant notes that the reference is directed to the use of *E. coli* DSM 6601 for its ability to enhance the systemic immune response against subsequent systemic infections with pathogenic bacteria or yeast. The prophylactic treatment or therapy of diarrhea caused by bacterial or fungal infections of the intestine by using DSM 6601 is not the subject of this reference. According to *Hockertz*, following an oral application of DSM 6601, mice were exposed to a systemic infection with pathogenic bacteria or yeast. Through the intravenously-applied pathogenic germs, a systemic infection occurs, but there is no reported infection of the duodenum or any associated diarrhea. By reason of the different application route, Applicant submits that the *E. coli* DSM 6601 and the causal agents of the infection are never in direct contact with each other. Such a situation is entirely different than in the case of an intestinal infection, wherein the causal agents and the *E. coli* DSM 6601 suspension are in direct contact with, and have a direct effect upon, each other. As such, *Hockertz* discloses a prophylactic method for a systemic disease, which is completely different from a gastro-intestinal disease, which is the focus of Applicant's invention. As such, it is plain that *Hockertz* does not teach or suggest the claimed invention.

It appears that the Examiner is attempting to overcome the deficiencies of the reference by contending that the one-step administration of DSM 6601 to mice in *Hockertz* would apparently necessarily and always prevent diarrhea and therefore anticipate the claimed methods. The Examiner seems to suggest, therefore, that because the reference is directed to a method for treating a systemic disease, it inherently teaches a method

for treatment of all diseases with *E. coli* strain DSM 6601. This is absolutely contrary to the case law. Anticipation requires that each and every element which is set forth in the claim is found, either expressly or inherently, in a single prior art reference. *In re Robertson*, 169 F.3d 743, 745, 49 U.S.P.Q.2d 1949 (Fed. Cir. 1999) (citation omitted). A reference may still anticipate if the element is inherent in its disclosure. *Id.* However, to establish inherency, the extrinsic evidence "must make clear that that missing descriptive matter is necessarily present in the thing described in the reference and that it would be so recognized by persons of ordinary skill." *Continental Can Co. v. Monsanto Co.*, 940 F.2d 1264, 1268, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991). Significantly, the Federal Circuit has held that inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* at 1269, 948 F.2d 1264, 20 U.S.P.Q.2d at 1749 (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981)). There is absolutely no actual evidence provided to support the legal conclusion of inherency. Therefore, it is improper to merely allege something is inherent and force Applicant to try to prove the negative.

Moreover, Applicant notes that if the Examiner was correct in applying the inherency rejection in this instance, the PTO would never issue patents on second medical uses for a drug. For example, a hypothetical patent 1 claims "a method for treating hypertension in a subject by administering an effective amount of aspirin." Hypothetical patent 2 claims "a method of treating atherosclerosis in a subject by administering an effective amount of aspirin." Patent 2 is clearly patentable over patent 1. New uses of known compositions or processes are patentable. Similarly, Applicant submits that antibiotics that

are effective against bacteria are not necessarily effective against fungi, and are consequently not used in practice for the treatment of mycoces, for example, fungi-induced diarrhea. Analogously, it was not expected from the outset that an antibacterially effective probiotic, such as *E. coli* DSM 6601 would prove to have a prophylactic or therapeutic effect upon diarrhea caused by fungi. As such, the contention that the method of *Hockertz* would inherently prevent diarrhea or the intestinal colonization of pathogenic bacteria is unfounded.

With respect to the *Lodinova-Zadnikova et al.* reference, this article merely discloses the administration of DSM 6601 to newborns and its potential use as a prophylactic for bacterial infections. The issue is the problem of prophylactic treatment against an undesired bacterial colonization in the gastro-intestinal tract of newborn babies through germs in their surroundings. The study investigated whether an oral application of DSM 6601 to newborn babies directly following birth might prevent, or at least reduce, a colonization of pathogenic bacteria. Bacteriological stool tests were performed. There was no search for fungi, nor does the publication make any reference to either fungi in the intestine, diarrhea potentially caused by these, or a related therapy. Moreover, none of the children included in the study were suffering from diarrhea or intestinal colonization of a pathogenic fungi. Plainly, this reference neither teaches or suggests that DMS 6601 may be used for the treatment or prevention of diarrhea or the intestinal colonization of pathogenic fungi. Moreover, there is nothing to suggest that the treatment disclosed in the reference would necessarily and always result in antimycotic activity for the prevention of diarrhea.

Again, as noted above to the *Hockertz* reference, to establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference and that it would be so recognized by persons of ordinary skill in the art. Plainly, the methods for treating or preventing the intestinal colonization of pathogenic fungi and diarrhea caused therefrom are neither taught nor inherent in the teachings of *Lodinova-Zadnikova et al.* As such, the reference cannot anticipate the claimed methods.

Finally, with respect to the Examiner's contention that DE 196 37 936 teaches the administration of NISSLE 1917 (DSM 6601) to treat an intestinal fungal infection, and therefore anticipates the claimed methods, Applicant respectfully traverses the rejection. Initially, Applicant again wishes to point out that the reference merely teaches a pharmaceutical preparation containing DSM 6601 coupled to the antimycotic nystatin. Significantly, the reference directs that the "bioadhesive component" (DSM 6601) should be coupled to the "effective substance" (nystatin), chemically or otherwise, to form the pharmaceutical preparation. The DSM 6601 is not administered alone or in its natural form. Instead, it is coupled to nystatin solely to prolong bioadhesion and extended retention time at the site of absorption and/or action. Whether DSM 6601 in this reference possesses an antimycotic effect of its own is questionable at best when it is coupled to the nystatin. The anti-*Candida* effect of DSM 6601 is certainly dependent upon the presence of living, metabolically-active bacterial cells, while its adhesion properties depend only upon the presence of adhesive cell structures. As such, the method taught in the reference does not necessarily provide anti-fungal activity. Moreover, Applicant submits that there are

substantial doubts whether the DSM 6601, which was altered through a physical or chemical bond to the nystatin, indeed still represents viable cells. Chemical reactions which lead to a chemical bond between microorganisms and effective substances often occur in conditions which also give rise to destruction of the microorganism. This would not influence the bioadhesive properties of the *E. coli* DSM 6601, but could very well substantially effect the activity of the *E. coli* DSM 6601 against other microorganisms. As such, the method taught in DE 196 37 936 does not teach administering a therapeutically effective amount of viable *E. coli* DSM 6601 as required in the currently pending claims. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

As it is believed that all of the objections and rejections set forth in the Official Action have been fully met, favorable reconsideration and allowance are earnestly solicited.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that she telephone Applicant's attorney at (908) 654-5000 in order to overcome any additional objections which she might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

Application No.: 09/554,835 Docket No.: HARMSEN 3.3-002

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made**".

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Respectfully submitted,

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Version With Markings to Show Changes Made

2. (THRICE AMENDED) A method for treating or preventing diarrhea ~~mediated by intestinal colonization of pathogenic fungi~~ in a mammal, comprising administering to the mammal a therapeutically effective amount of viable *Escherichia coli* strain DSM 6601.

5. (TWICE AMENDED) A method for treating diarrhea mediated by pathogenic fungi in a mammal which suffers from intestinal colonization of the pathogenic fungi, comprising administering to the mammal a therapeutically effective amount of viable *Escherichia coli* strain DSM 6601.

6. (AMENDED) A method for preventing diarrhea ~~mediated by intestinal colonization of pathogenic fungi~~ in a mammal, comprising administering to the mammal a therapeutically effective amount of viable *Escherichia coli* strain DSM 6601.

6. (AMENDED) The method of claim 2, further comprising administering the *Escherichia coli* strain DSM 6601 for at least about 10 days.

8. (AMENDED) The method of claim 3, further comprising administering the *Escherichia coli* strain DSM 6601 for at least about 10 days.

10. (AMENDED) The method of claim 4, further comprising administering the *Escherichia coli* strain DSM 6601 for at least about 10 days.